

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 September 2000 (08.09.2000)

PCT

(10) International Publication Number
WO 00/52015 A3

(51) International Patent Classification⁷: C07F 9/6584

(21) International Application Number: PCT/US00/05672

(22) International Filing Date: 3 March 2000 (03.03.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/123,013 5 March 1999 (05.03.1999) US
60/153,127 8 September 1999 (08.09.1999) US

(71) Applicant: METABASIS THERAPEUTICS, INC.
[US/US]; 9390 Towne Centre Drive, San Diego, CA 92121 (US).

(72) Inventors: ERION, Mark, D.; 13455 Mango Drive, Del Mar, CA 92104 (US). REDDY, K., Raja; 4146 Federman Lane, San Diego, CA 92130 (US). BOYER, Serge, H.; 5112 Castle Hills Drive, San Diego, CA 92109 (US).

(74) Agents: WOLFF, Jessica, R. et al.; Brobeck, Phleger & Harrison, 12390 El Camino Real, San Diego, CA 92130 (US).

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

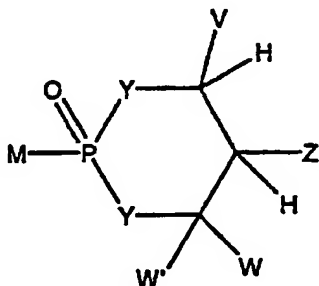
Published:

— With international search report.

(88) Date of publication of the international search report:
15 February 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL PHOSPHORUS-CONTAINING PRODRUGS



(I)

(57) Abstract: Novel cyclic phosphoramidate prodrugs of drugs of formula (I) of parent drugs MH their use in delivery of drugs to the liver, their use in enhancing oral bioavailability, and their method of preparation are described.

WO 00/52015 A3

INTERNATIONAL SEARCH REPORT

I. International Application No
PCT/US 00/05672

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F9/6584

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 072 531 A (MAX PLANCK GESELLSCHAFT ;BEHRINGWERKE AG (DE)) 23 February 1983 (1983-02-23)	1-3, 11-13, 17,18, 20,31, 42,70, 97,126, 158
X	page 1, line 5 - line 25; claims 1-6; examples 6,7,13-28 page 3, line 15 - line 25	84
X	EP 0 002 062 A (MAX PLANCK GESELLSCHAFT) 30 May 1979 (1979-05-30)	1,20
X	page 10, line 21 -page 15, line 15	70,84, 107
X	page 5, line 22 -page 2, line 22 --- -/--	150

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

17 October 2000

Date of mailing of the international search report

15. 11. 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Richter, H

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/05672

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 261 283 A (APPLIED BIOSYSTEMS) 30 March 1988 (1988-03-30) claims 21-28	161
X	CH 492 738 A (SANDOZ AG) 30 June 1970 (1970-06-30) the whole document	1-3, 11-13, 17,18, 20,97, 121,126, 138
X	WO 98 09668 A (ATTARD GEORGE SIMON ;RILEY. PATRICK ANTHONY (GB); MCGUIGAN CHRISTOP) 12 March 1998 (1998-03-12) page 24; table 4 page 1	1-3, 11-13, 20, 32-34, 97,121, 126,138
X	EP 0 158 057 A (ASTA WERKE AG CHEM FAB) 16 October 1985 (1985-10-16) page 1 -page 2; claims 1-8; examples 1-6	1-38,97, 121,126, 138
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 01, 30 January 1998 (1998-01-30) & JP 09 241284 A (YAMASHITA KOJI;NIPPON SODA CO LTD), 16 September 1997 (1997-09-16) abstract	1,11,12, 18
X	NIFANT'EVE. ET AL.: "1,3,2,-DIAZAPHODSPHORINANES" ZH. OBSHCH. KHIM., vol. 49, no. 1, 1979, pages 64-74, XP002150298 page 67	1-3,19
A	DE 16 93 219 A (BASF AG) 17 September 1970 (1970-09-17) example 1	1-20,47

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/05672

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 58-109, 112-149, 110, 111, 167-175
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 168-175, 89-96
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 110 and 111 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 58-88, 97-109, 112-149 are directed to a method of treatment of the animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 58-109, 112-149, 110, 111, 167-175

110, 111: Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

58-109, 112-149: Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box I.2

Claims Nos.: 168-175, 89-96

Claim 89 shows a compound which is designated "formula I" but differs from formula I as shown in claim 1. Furthermore the compound of claim 89 does not contain P, but 6 binding N. Hence, the scope of claims 89-96 is obscure.

The category of the two claims 168 is not clear (prodrug or use of compound of formula I ?).

The category of claims 169-175 is not clear (product or process?)

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: completely 22-26,38-41,47,
49-57; partially claims 1-21,27-30,32-37,46,48,
58-88,97-166

Compounds of formula I in which Z is H (W and V are connect or not) their preparation, use and intermediates

2. Claims: partially 1-22,27-30,32-37, 46,48,58-88,97-166

Compounds of formula I in which Z is connected to the cycle via O, S, N (Z = OR, SR etc.), (W and V are connected or not), their preparation, use and intermediates

3. Claims: completely 30, 31, 42-45 partially claims 1-22,
27-30,32, 35-37,46,48,58-88,97-166

Compounds of formula I in which Z is connected to the cycle via a carbon atom, (W and V are connect or not), their preparation, use and intermediates

4. Claims: partially 1-19, 58-88, 97-166

Compounds of formula I in which Z and V are connected, their preparation, use and intermediates

5. Claims: partially 1-29, 58-88, 97-166

Compounds of formula I in which Z and W are connected, their preparation, use and intermediates

6. Claims: partially claims 1-19,58-88,97-166

Compounds of formula I in which W' and W are connected, their preparation, use and intermediates

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/05672

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0072531	A	23-02-1983	DE 3132221 A AU 8717082 A DK 364782 A ES 514852 D ES 8400752 A JP 58041892 A PT 75416 A,B ZA 8205876 A	19-05-1983 17-02-1983 15-02-1983 01-11-1983 01-02-1984 11-03-1983 01-09-1982 29-06-1983
EP 0002062	A	30-05-1979	DE 2752125 A AT 382623 B AT 267781 A AT 368166 B AT 807578 A DK 518478 A IT 1101418 B JP 54081224 A	23-05-1979 25-03-1987 15-08-1986 27-09-1982 15-01-1982 23-05-1979 28-09-1985 28-06-1979
EP 0261283	A	30-03-1988	WO 8802004 A US 4757141 A JP 6102670 B JP 1500748 T US 5212304 A US 5258538 A	24-03-1988 12-07-1988 14-12-1994 16-03-1989 18-05-1993 02-11-1993
CH 492738	A	30-06-1970	NONE	
WO 9809668	A	12-03-1998	AU 4128597 A	26-03-1998
EP 0158057	A	16-10-1985	AT 42558 T CA 1254903 A DD 234017 A DE 3505482 A DE 3569737 D DK 93985 A ES 540777 D ES 8607332 A ES 540778 D ES 8602831 A FI 850800 A,B, GR 850501 A HU 36829 A IE 57950 B JP 1973637 C JP 7002757 B JP 60222494 A KR 8903789 B PL 252161 A PT 80024 A,B US 4716242 A YU 31285 A YU 120287 A ZA 8501062 A	15-05-1989 30-05-1989 19-03-1986 05-09-1985 01-06-1989 02-09-1985 16-05-1986 01-11-1986 01-12-1985 16-03-1986 02-09-1985 26-06-1985 28-10-1985 19-05-1993 27-09-1995 18-01-1995 07-11-1985 04-10-1989 26-08-1986 01-03-1985 29-12-1987 29-02-1988 30-04-1988 27-11-1985
JP 09241284	A	16-09-1997	NONE	
DE 1693219	A	17-09-1970	BE 633481 A FR 1360130 A	12-08-1964

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 00/05672

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 1693219	A	GB 987378	A